No. 08-437

IN THE

Supreme Court of the United States

JOSEPH C. COLACICCO, INDIVIDUALLY
AND AS EXECUTOR OF THE ESTATE OF
LOIS ANN COLACICCO, DECEASED,
AND
BETH ANN MCNELLIS, ON BEHALF OF THE
ESTATE OF THEODORE DEANGELIS,
DECEASED, AND IN HER OWN RIGHT,

Petitioners,

v.

APOTEX, INC.; APOTEX CORP., A SUBSIDIARY OF APOTEX, INC.;
SMITHKLINE BEECHAM D/B/A GLAXOSMITHKLINE;
AND PFIZER INC.

Respondents.

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Third Circuit

RESPONDENT PFIZER INC.'S BRIEF IN OPPOSITION

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QUESTION PRESENTED

Repeatedly before, and shortly after, Petitioner Beth Ann McNellis's decedent committed suicide while being treated with Respondent Pfizer Inc.'s antidepressant medication Zoloft, the Food and Drug Administration (i) concluded that scientific evidence did not show that Zoloft increases the risk of suicidality, (ii) specified the warnings that Pfizer was required to provide regarding suicidality, and (iii) directed Pfizer not to use any different suicidality warnings. Did the Third Circuit correctly conclude that, under these regulatory facts, conflict preemption bars a state-law claim that Pfizer should have warned that Zoloft does increase the risk of suicidality?

PARTIES TO THE PROCEEDING

The United States Court of Appeals for the Third Circuit consolidated for oral argument the appeals from two different district courts' preemption decisions and issued a single decision in the two cases. Petitioner Beth Ann McNellis, who claims that her father committed suicide due to his use of Pfizer Inc.'s antidepressant Zoloft, was the plaintiff and appellant below in *McNellis v. Pfizer Inc.* Petitioner Joseph C. Colacicco, who claims that his wife committed suicide due to use of GlaxoSmithKline's antidepressant Paxil, was the plaintiff and appellee below in *Colacicco v. Apotex Inc.* This is Pfizer's response to Petitioner McNellis's petition.

RULE 29.6 CORPORATE DISCLOSURE STATEMENT

Respondent Pfizer is a publicly traded corporation. It has no parent corporation, and no publicly held company owns ten percent or more of its stock.

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The Third Circuit determined that, under the particular, highly unusual facts surrounding FDA's suicidality warning requirements for Pfizer's antidepressant Zoloft, Petitioner McNellis's claim that New Jersey product liability law required different suicidality warnings conflicts with, and is therefore preempted by, those federal requirements. The facts presented to the Third Circuit show that FDA, for

more than 15 years, continually considered whether Zoloft and other antidepressants in the class called selective serotonin reuptake inhibitors ("SSRIs") were associated with an increased risk of suicidality in adult patients. FDA repeatedly determined that the scientific evidence did not support such an association and that suicidality warnings more dire than those required by FDA could actually harm patients suffering from depression. FDA made and repeated those determinations many times before, and shortly after, McNellis's decedent, Theodore DeAngelis, used Zoloft.

McNellis seeks review by this Court and requests that the Court grant her petition or hold it pending resolution of *Levine v. Wyeth*, 944 A.2d 179 (Vt. 2006), *cert. granted*, 128 S. Ct. 118 (2008) (No. 06-1249) (argued Nov. 3, 2008). The Court should do neither.

1. The issue in *Levine* differs from the issue in this case, and the Third Circuit's decision in this case is correct regardless of whether *Levine* is affirmed or reversed. As the Third Circuit noted after summarizing the facts on which the Vermont Supreme Court based its finding of no preemption in *Levine*, "The facts in these [consolidated] cases are otherwise." *Colacicco v. Apotex Inc.*, 521 F.3d 253, 272 n.17 (3d Cir. 2008). The Vermont Supreme Court in *Levine* based its no-preemption ruling on a finding that FDA (a) had not considered whether there was reasonable scientific evidence supporting the type of warning proposed by the plaintiff for an anti-nausea medicine and (b) had not determined that warnings of that type should not be given. Here, in contrast, the Third Circuit recognized that FDA (a) ***had*** considered

whether there was reasonable scientific evidence supporting the type of warning proposed by McNellis for Zoloft and (b) ***had*** determined that warnings of that type should not be given. 521 F.3d at 272 & n.17. Thus, in deciding *Levine*, this Court need not address the preemption issue in this case.

2. McNellis also erroneously suggests that the Third Circuit's decision presents two open questions of federal law: (a) Whether the presence or absence of conflict preemption should be determined based on a federal regulatory requirement that did not exist until after the relevant period, rather than on the one that existed during the relevant period, and (b) whether individual courts, rather than FDA, should decide in the first instance if information allegedly withheld from FDA would have caused the agency to impose requirements different from the requirements it actually did impose. Neither of these is an open question of law, and the Third Circuit correctly ruled in accordance with well-established principles of conflict preemption and primary jurisdiction.

3. In any event, review is not warranted, because the Third Circuit's decision is correct. It is so plainly correct that, instead of addressing the decision, McNellis posits a straw man by contending that the Third Circuit found preemption based merely on the possibility that Pfizer's unilateral implementation of the warnings she advocates might have resulted in prosecution under the Federal Food, Drug, and Cosmetic Act for "misbranding." She then attacks that straw man by arguing that that conflict was impermissibly hypothetical.

The actual basis of the Third Circuit's ruling, however, was the direct, real conflict between (a)

McNellis's claim that New Jersey law required warnings stating that Zoloft is associated with adult suicidality and (b) FDA's requirement—based on its repeated finding of no reasonable evidence of such an association—that the FDA-mandated suicidality warnings, and no other, be given. Whether a successful misbranding action would have been brought had Pfizer disobeyed FDA's requirement is immaterial to the Third Circuit's decision.

Furthermore, FDA's decision to require specified warnings about suicidality, to require that Zoloft's labeling language for suicidality be "identical" to FDA's specified language, and to prohibit any other suicidality warning was not a decision "not to regulate." Therefore, contrary to McNellis's contention, this Court's reasoning in *Sprietsma v. Mercury Marine*, 537 U.S. 51 (2002), supports preemption in this case.

STATEMENT OF THE CASE

A. FDCA and FDA Labeling Requirements

The Federal Food, Drug, and Cosmetic Act ("FDCA") requires that prescription medicines be approved as "safe and effective" by FDA before being sold. 21 U.S.C. §§ 355(d), 393(b)(2)(B). To obtain FDA approval, a manufacturer must submit a new drug application ("NDA") containing results of laboratory, animal, and human tests; results of clinical studies; and extensive additional information. *Id.* § 355(b), (d).

Accordingly, FDA will deny an NDA if test results "show that the drug is unsafe for use under the conditions prescribed, recommended, or suggested in

its proposed labeling or the results do not show that the drug product is safe for use under those conditions," or if "[t]here is insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling." 21 C.F.R. § 314.125(a), (b)(3)-(4); *see* 21 U.S.C. § 355(d).[1] FDA approves an NDA only if the agency "determines that the drug meets the statutory standards for safety . . . and labeling[.]" 21 C.F.R. § 314.105(c); *see also* 50 Fed. Reg. 7452-01, 7470 (Feb. 22, 1985) ("[L]abeling serves as the standard under which FDA determines whether a product is safe and effective."). The same requirements apply whenever the manufacturer of a medication approved for treatment of one illness seeks to market it as a treatment for an additional illness. 21 C.F.R. §§ 314.54, 314.70, 314.71.

FDA regulations mandate the format and content of four labeling categories—"Contraindications," "Warnings," "Precautions," and "Adverse Reactions"—and the risk information each must contain. *Id.* §§ 201.56, 201.57. FDA specifies its product-specific labeling requirements in an "approvable" letter telling the manufacturer that an NDA will be approved if the manufacturer satisfies specified conditions. *Id.* § 314.110(a). Final approval is "conditioned upon the applicant incorporating the specified labeling changes exactly as directed, and upon the applicant submitting to FDA a copy of the final printed labeling prior to marketing." *Id.* § 314.105(b).

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[1] Citations to 21 C.F.R. are to regulations in effect on the date of Mr. DeAngelis's demise.

After final approval, FDA continues to monitor the medication's safety, including the labeling's adequacy. The FDCA requires FDA to withdraw approval whenever it finds "a lack of substantial evidence that the drug will have the effect it purports or is represented to have," and allows FDA to withdraw approval upon finding labeling "false or misleading in any particular." 21 U.S.C. § 355(e).

B. FDA's Initial Approval of Zoloft as Safe and Effective with the FDA-Mandated Suicidality Warnings That McNellis Claims Were Inadequate

On April 13, 1988, Pfizer submitted to FDA an NDA seeking approval to market Zoloft to treat adult depression. Because of a controversy regarding another SSRI antidepressant, Prozac, FDA directed Pfizer to provide a detailed report of all suicidality during Zoloft clinical trials. (JA 277-359.)[2] Pfizer included the report in the NDA. (*Id.*)

On November 19, 1990, FDA convened its Psychopharmacologic Drugs Advisory Committee to review the NDA and advise FDA regarding Zoloft's safety and efficacy. (JA 360-490.) The Advisory Committee consisted of psychiatrists, statisticians, and other experts chosen by FDA from academic and research institutions throughout the nation. (JA 362-364.)

The Advisory Committee received extensive presentations of scientific data and analyses, including presentations by FDA officials who had studied Zoloft clinical-trial safety data, efficacy data, and sta-

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[2] Citations to "JA" are to the Joint Appendix below.

tistical analyses. (JA 366-397.) The FDA official who presented the safety data concluded that "disproportionate numbers of suicide attempts do not occur [in clinical trials]." (JA 389.) The Advisory Committee then voted unanimously that the evidence showed that Zoloft "is safe when used in the treatment of depression." (JA 476.)

Accordingly, FDA issued its Zoloft "approvable" letter on September 30, 1991. (JA 491.) It included labeling that FDA said "presents a fair summary of the information available on the benefits and risks of [Zoloft]." (*Id.*) FDA directed Pfizer to "use the proposed text verbatim." (*Id.*) The "Precautions" section required by FDA included the following:

> Suicide – The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high risk patients should accompany initial drug therapy. Prescriptions for Zoloft (sertraline) should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

(JA 499-500.) The "Adverse Reactions" section required by FDA defined "infrequent adverse events" as "those occurring in 1/100 to 1/1000 patients," listed "suicide attempt" as "infrequent," and stated, "It is important to emphasize that although the events reported occurred during treatment with Zoloft (sertraline), they were not necessarily caused by it." (JA 508-509.) Thus, FDA required labeling that (a) informed physicians of the suicidality rate during

clinical trials, (b) stated FDA's conclusion that the rate did not differ enough from the suicidality rate for patients given placebo to warrant a finding of an association between Zoloft and suicidality, and (c) enabled physicians to exercise their professional judgment on how best to use this information when treating their patients.

FDA granted final approval of the Zoloft NDA on December 30, 1991. (JA 513-530.)

C. FDA's Rejection of Two Petitions Seeking Changes in Prozac Labeling Regarding Suicide

While evaluating the Zoloft NDA, FDA also was studying claims that Prozac causes suicide. In February 1990 a Dr. Martin Teicher published an article stating that six patients had reported suicidal thoughts after several weeks of Prozac treatment. (JA 590-593.) The article started a controversy over the possible causes. (JA 594-623.)

On October 11, 1990, the Church of Scientology's "Citizens Commission on Human Rights" filed a petition claiming that Prozac caused suicidality and asking FDA to withdraw approval of Prozac. (JA 624-633.) On May 23, 1991, representatives of "Public Citizen Health Research Group" ("PCHRG") filed a petition citing Teicher and asking FDA to add to Prozac's labeling a warning "regarding its association with intense, violent suicidal preoccupation, agitation, and impulsivity in a small minority of patients." (JA 634-643.)

On July 26, 1991, FDA denied the Scientology petition, stating, "The data and information available at this time do not indicate that Prozac causes sui-

cidality or violent behavior." (JA 644-664.) The agency noted that the Teicher article failed to disclose important facts—including histories of unremitting depression and suicidal thoughts and acts—that "do not permit a conclusion that Prozac caused the obsessive suicidality." (JA 650.) FDA also stated that, to address the issue more broadly, it would ask its Psychopharmacologic Drugs Advisory Committee "to consider the issue of suicidality associated with all antidepressant drug products." (JA 664.)

On September 20, 1991, FDA convened its Advisory Committee for a "scientific investigation into suicidal ideation, suicidal acts, and other violent behavior reported to occur in association with the pharmacological treatment of depression." (JA 674-675.) Again, the Advisory Committee included FDA-invited psychiatrists and scientists from academic and research institutions. (JA 669-671.)

The Advisory Committee investigated "the possibility of a causal linkage between the emergence and/or intensification of suicidal thoughts and acts, suicidality, that is, and/or other violent behaviors and the use of antidepressant drugs." (JA 787.) Dr. Paul Leber, Director of FDA's Division of Neuropharmacological Drug Products, emphasized:

> [A]ny consideration of the need for additional regulatory action must begin with appreciation of the fact that suicidal thoughts, acts, and other violent behaviors are common manifestations of psychiatric syndromes for which antidepressants are prescribed . . . . [I]t is not ordinarily possible to determine from the facts of a particular case history, no

> matter how compelling, that it involves an untoward response to an antidepressant drug, no matter how tragic the outcome of that case, whether the particular outcome is a consequence of drug treatment or simply a manifestation of the nonresponding underlying psychiatric condition.

(JA 789-790.) Referring to controlled clinical studies, Dr. Leber further stated: "[E]valuation of such sources, at least to date, evaluation by FDA scientists, outside consultants, and by our physicians, have not led us to conclude that there is a differential rate of risk for Prozac related to suicidal thoughts, acts, or other violent behaviors." (JA 791.)

Most importantly, FDA's Dr. Leber cautioned that

> the net effect [of language saying that antidepressants cause suicide] might be a reduction in the use of antidepressants in the treatment of depression, and that result might cause overall injury to the public health. . . . We all have to remember that the best-intentioned of actions do not necessarily turn out well; they can cause harm.

(JA 794-795.) He then made several additional points: (i) The precautions for all antidepressants' labeling already "[made] clear that prescribers ought to be aware that depression is a serious illness that carries with it the risk of suicide and that in the period following the initiation of treatment great care

must be taken to supervise patients and monitor them closely"; (ii) FDA would continue to monitor and evaluate all marketed drugs and would take further action if any "signal of potential concern" were identified; and (iii) "modifying antidepressant drug labeling" could be "false and misleading." (JA 788-798 & 1290.) Another FDA physician-scientist, Dr. Thomas Laughren, further explained FDA's "lack of confidence in a causal link between the taking of the drug and [suicidal] behaviors." (JA 802.)

The Advisory Committee then answered three questions for FDA. As to whether "[t]here is credible evidence to support a conclusion that antidepressant drugs cause the emergence and/or intensification of suicidality and/or other violent behaviors," it unanimously voted there was not. (JA 959.) As to whether "there is evidence to indicate that a particular drug or drug class poses a greater risk for the emergence and/or intensification of suicidal thoughts and acts and/or other violent behaviors," it unanimously voted there was not. (JA 967.) As to whether there should be a labeling change for all antidepressants, it voted six-to-three there should not. (JA 996.)

FDA denied the PCHRG petition on June 3, 1992, finding the evidence insufficient to support a warning of an "association with intense, violent suicidal preoccupation, agitation, and impulsivity in a small minority of patients." (JA 1008.)

D. FDA's Repeated Rejections, Before and After DeAngelis's Demise, of Warnings Saying That Zoloft Causes Suicide

During the ensuing decade, FDA continued to study Zoloft, examine additional suicidality data, and

find no evidence meeting the requirements of 21 C.F.R. section 201.57(e) for warning of an association between Zoloft and suicide. Instead, FDA made six more determinations that Zoloft was "safe and effective" with the FDA-required suicidality warnings in the "Precautions" and "Adverse Reactions" sections of the labeling. Specifically, FDA found Zoloft, as thus labeled, safe and effective in 1996 (for adult obsessive compulsive disorder, or "OCD"); in 1997 (for panic disorder and pediatric OCD) (JA 1051-1079, 1080-1110); in 1999 (for post-traumatic stress disorder); in May 2002, only seven months before DeAngelis's demise (for premenstrual dysphoric disorder); and on February 7, 2003, only eight days after DeAngelis's demise (for social anxiety disorder). (JA 1175-1212.) In each instance, FDA sent Pfizer a letter specifying the required language and location for suicidality warnings; in each instance, FDA directed Pfizer that Zoloft labeling must be "identical" to what FDA specified; and the suicidality warnings that FDA reconfirmed and required before and after January 2003 are the warnings that McNellis now claims were inadequate at that time. (JA 1027, 1052, 1082, 1111, 1140, 1175.)

E. FDA's Rejection of a Third Petition Claiming That Prozac Causes Suicide

On January 2, 1997, a Ms. Rosellen Meysenburg filed a citizen's petition asking FDA to require Prozac warnings that "people who are considered at risk for suicide and who begin to take [Prozac] should be carefully observed and should consider taking a sedative as well." (JA 1280-1282.) On June 25, 1997, FDA denied the petition, stating: "The agency has continued to monitor carefully reports of a possible

connection between Prozac and increased suicidality. However, no credible scientific evidence has caused the agency to depart from its conclusion that the current Prozac labeling appropriately reflects the level of concern about Prozac and suicidality." (JA 1283-1284.)

F. FDA's 2002 Brief Reaffirming That There Still Was No Reasonable Evidence of an Association Between Zoloft and Suicide

In September 2002, just four months before DeAngelis took Zoloft, FDA again reaffirmed its opposition to warnings suggesting that Zoloft causes suicide. In an *amicus* brief in *Motus v. Pfizer Inc.*, Nos. 02-55372 & 02-55498 (9th Cir. Sept. 4, 2002) ("2002 Zoloft *amicus* brief") (JA 241-272), FDA noted that its recent further review of the suicidality issue had again discerned no scientific basis for such a warning. The agency stated, "To require a warning of a supposed danger that ***FDA concludes has no actual scientific basis***, no matter the warning's language, would be to require a statement that would be false or misleading, and thus contrary to federal law." (JA 246-247 (emphasis added).) FDA also noted that permitting claims based on a scientifically unsupported causal association between Zoloft and suicide would frustrate the FDCA's purposes and objectives by over-deterring the use of beneficial, potentially lifesaving therapy. (JA 268.) Therefore, FDA said, the state-law claims should be held preempted.[3]

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[3] The *Motus* district court granted summary judgment for Pfizer on other grounds, *see Motus v. Pfizer Inc.*, 196 F. Supp. 2d 984 (C.D. Cal. 2001), *aff'd*, 358 F.3d 659 (9th Cir. 2004), after

G. FDA's 2003 Reaffirmations That Zoloft Was Safe and Effective with the FDA-Mandated Labeling

Five months after DeAngelis's demise, FDA completed another review of pediatric and adolescent adverse-event data for Zoloft, including reports of suicidal thoughts or behavior. (JA 1434-1435.) On June 12, 2003, FDA concluded that the evidence still did not "provide any safety signals that indicate that the Agency needs to do anything except continue to actively assess the evolving benefit-risk profile of these products." (JA 1434.) Also in 2003, FDA again found no increased suicide risk associated with the use of antidepressants to treat adult depression. *See* T. Hammad, *et al.*, *Incidence of Suicide in Randomized Controlled Trials of Patients with Major Depressive Disorder*, 12 Pharmacoepidemiology & Drug Safety S156 (2003).

H. The FDA Commissioner's March 2004 Reaffirmation of Intended Preemption of Claims Like McNellis's

On March 11, 2004, the FDA Commissioner testified before Congress and discussed FDA's longstanding involvement in preemption issues, including its 2002 Zoloft *amicus* brief. (JA 1291-1302.) The Commissioner reaffirmed the agency's intent to preempt the warning claim in *Motus* because "FDA had

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denying Pfizer's preemption motion, *see Motus v. Pfizer Inc.*, 127 F. Supp. 2d 1085 (C.D. Cal. 2000). The plaintiff appealed, and Pfizer cross-appealed the denial of its earlier summary judgment motion. The United States filed its *amicus* brief in support of Pfizer's preemption argument. The Ninth Circuit affirmed the judgment for Pfizer without addressing preemption.

specifically considered, and rejected, the language requested [for Zoloft] by the plaintiff under state law." (JA 1299.)

I. FDA's Continuing Consideration of the Scientific Evidence, and Amendments to FDA Requirements for Antidepressant Warnings

On March 22, 2004, FDA stated in a Public Health Advisory that it remained unclear whether any antidepressants "contribute to the emergence of suicidal thinking and behavior." (JA 1303-1305.) While FDA continued to reexamine data for a variety of antidepressants, however, it requested that the warning for all antidepressants be modified to "recommend[] close observation of adult and pediatric patients treated with these agents for worsening depression or the emergence of suicidality" and be moved from the labeling's "Precautions" section to the "Warnings" section. (*Id.*) In January 2005, based on a new analysis of "pooled" clinical-trial data for nine different antidepressants, FDA directed ***all*** manufacturers of ***all*** antidepressants to add new suicidality warnings, including a "black-box" warning for pediatric patients. (JA 1353-1362.)

Although the preemption issue here turns on the warnings required by FDA when DeAngelis was treated with Zoloft in January 2003, the March 2004 Public Health Advisory and the January 2005 directive show that FDA continued to monitor the suicidality issue and to require the warnings that the agency found supported by scientific evidence.

J. FDA's Reiterations of Why Claims Such as Plaintiff's Conflict with FDA's Purposes and Policies

In an *amicus* brief in another Zoloft case in September 2005 ("2005 Zoloft *amicus* brief"), FDA reaffirmed and further explained the positions taken in its 2002 Zoloft *amicus* brief:

> The United States hereby reaffirms the points made in its *Motus* brief . . . . [T]he Government's position is that the state tort law claims in this case—under which the plaintiffs argue that defendant Pfizer should be liable for using only the labeling for Zoloft approved by FDA—are preempted because they would punish Pfizer for not using a label that, as of November 2002, would have misbranded the drug.

(JA 1496.) FDA again identified the safety policies underlying its refusal to allow warnings that it had determined lacked reasonable scientific support:

> [I]n the realm of warnings with regard to prescription drugs, more is not always better. Requiring additional warnings for a medication is not the same as requiring that it meet a higher level of safety. Mandating an additional warning for a medication will be beneficial to public health only if that warning reflects a scientifically supportable additional danger.

(JA 1520.) FDA cited extensive evidence showing that, beginning before Zoloft was approved in 1991 and continuing to the date of the brief in 2005, it had considered, and found no reasonable evidence of, an association between Zoloft and suicidality. (JA 1535-1714.)

On January 24, 2006, FDA published a Final Rule titled "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products" ("Final Rule"). The preamble (i) described the purposes and policies underlying the agency's regulations governing prescription medicine labeling and (ii) explained why the agency believed that pre-emption should apply in certain inadequate-warning cases. 71 Fed. Reg. 3922, 3933-36, 3967-69 (Jan. 24, 2006) (the "January 2006 Preamble").

The preamble addressed the situation where, as here, FDA has specifically considered and rejected the warning a plaintiff advocates. It stated:

> FDA believes that State laws conflict with and stand as an obstacle to achievement of the full objectives and purposes of Federal law when they purport to compel a firm to include in labeling or advertising a statement that FDA has considered and found scientifically unsubstantiated.

Id. at 3935. FDA explained that this must be so because state-law imposition of additional warning requirements "can erode and disrupt the careful and truthful representation of benefits and risks that prescribers need to make appropriate judgments about drug use." *Id.*

FDA also disputed the suggestion that 21 C.F.R. section 314.70(c)—the regulation that under some circumstances allows a manufacturer to strengthen a warning while seeking FDA approval of the stronger warning—totally negates the preemptive effect of FDA's labeling requirements, even where FDA has concluded that scientific evidence does not support the stronger warning. The agency explained that such an interpretation "conflict[s] with the agency's own interpretations" of its own regulations and "frustrate[s] the agency's implementation of its statutory mandate." 71 Fed. Reg. at 3934.

K. FDA's 2007 Confirmation of Its Finding of No Association Between SSRIs and Adult Suicidality

On May 2, 2007, FDA announced that it had completed a review of adult suicidality data for nine antidepressants, including Zoloft, and had concluded that "scientific data did not show [an increased suicidality] risk in adults older than 24, and that adults ages 65 and older taking antidepressants have a decreased risk of suicidality." (*See* 5/2/07 FDA Press Release, *available at* http://www.fda.gov/bbs/topics/NEWS/2007/NEW01624.html.) The agency therefore required that the labeling for all antidepressants, including Zoloft, be revised to state that "[s]hort-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction [in risk] with antidepressants compared to placebo in adults aged 65 and older." (*See* 5/2/07 Revisions to Product Labeling, *available at* http://www.fda.gov/cder/drug/antidepressants/default.htm.) The current FDA-mandated label for Zoloft therefore states that SSRIs

are not associated with an increased risk of suicidality in individuals in DeAngelis's age group.[4]

REASONS FOR DENYING THE WRIT

I. THERE IS NO DIVISION IN APPELLATE AUTHORITY ON THE QUESTIONS THE PETITION PRESENTS

A. No Federal Court of Appeals Other Than the Third Circuit in This Case Has Ruled on the Preemptive Effect of the Type of Conflict Present Here

McNellis seeks to hold Pfizer liable for not providing suicidality warnings of a type that, repeatedly before DeAngelis's demise and again only eight days after it, FDA found unsupported by scientific evidence. When FDA initially approved Zoloft for marketing, it mandated that Zoloft labeling address suicidality by using "verbatim" the language the agency specified, including the statement that some suicidality events had "occurred during treatment with Zoloft," but "were not necessarily caused by it." Moreover, on September 20, 1991, only ten days before FDA issued its "approvable" letter for Zoloft, the agency's Director of the Division of Neuropharmacological Drug Products explained ***why*** a different suicidality warning for antidepressants would impair federal objectives—namely, the result "might be a reduction in the use of antidepressants in the treatment of depression, and that result might cause overall injury to the public health."

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[4] DeAngelis was 64 when he used Zoloft.

FDA subsequently approved Zoloft six times as "safe and effective" for the treatment of other psychiatric disorders. Each time FDA reexamined the labeling, it directed that the suicidality warnings add a reference to the additional disorder, but insisted that the suicidality language remain the same in all other respects and mandated that the language be "identical to" that specified by the agency. FDA issued one such directive on May 16, 2002, only seven months before DeAngelis's demise, and another on February 7, 2003, just eight days after his demise. Even in 2007, after reviewing data for nine different antidepressants, including Zoloft, FDA concluded that "scientific data did not show [an increased suicidality] risk in adults older than 24, and that adults ages 65 and older taking antidepressants have a decreased risk of suicidality."

FDA's repeated conclusion, both shortly before and just after DeAngelis's demise, that there was no reasonable evidence of an association between Zoloft and suicidality, shows that Pfizer could not, without violating applicable FDA regulations, have added between those dates a warning asserting such an association. *See* 21 C.F.R. § 210.57(e) (requiring "reasonable evidence of an association" before including a warning in the "Warnings" category of a label); *cf.* 44 Fed. Reg. 37434, 37447 (June 26, 1979) ("[T]he decision as to whether a warning is legally required for the labeling of a drug must rest with the agency."). The Third Circuit based its decision on this specific, unique set of regulatory actions. *See* 521 F.3d at 271 ("a state-law obligation to include a warning asserting the existence of an association between SSRIs and suicidality directly conflicts with FDA's oft-repeated conclusion that the evidence did not support

such an association"); *cf. Dusek v. Pfizer Inc.*, No. Civ.A. H-02-3559, 2004 WL 2191804 (S.D. Tex. Feb. 20, 2004) (finding that federal law preempted a claim that Pfizer inadequately warned of Zoloft suicide danger, and noting that "the facts before this Court are unique").

B. *Levine* Presents Issues Materially Different from Those in This Case

FDA's continual evaluation, for more than 15 years, of the precise question whether SSRIs are associated with increased adult suicidality, and its repeated conclusion that they are not, creates a vital distinction between this case and *Levine*. McNellis therefore is wrong in contending that this Court's decision in *Levine* will be determinative of the preemption issues presented here.

Wyeth argued in *Levine* that the plaintiff's claim that Wyeth should have provided a stronger warning concerning "IV push" administration of the antinausea medicine Phenergan was preempted because "FDA prohibited the use of a stronger warning with respect to IV-push administration." *Levine*, 944 A.2d at 188. The Vermont Supreme Court found no preemption because "[t]he record lacks any evidence that the FDA was concerned that a stronger warning was not supported by the facts, that such a stronger warning would distract doctors from other provisions in the drug's label, or that the warning might lead to less effective administration of the drug." *Id.*; *see also id.* at 189 ("Neither the letters nor any other evidence presented to the jury indicated that the FDA wished to preserve the use of IV push as a method of administering Phenergan.").

Here, in contrast, as the Third Circuit found, FDA considered and rejected claims that SSRIs are associated with adult suicidality and that SSRI labels should warn of such an association. 521 F.3d at 272 n.17 (noting that, in contrast to the Vermont Supreme Court's finding of no evidence that FDA considered or prohibited a stronger IV-push warning, "[t]he facts in these cases are otherwise"). Thus, the Third Circuit's decision does not conflict with *Levine*. If this Court reverses in *Levine*, the correctness of the Third Circuit's decision will be even more readily apparent than it already is; and if this Court affirms *Levine*, the crucial difference between the regulatory facts there and the regulatory facts here will ensure that the holding there will not affect the Third Circuit's holding here.

Because there is no division in appellate authority to be resolved by certiorari review, the petition should be denied.

II. THE ISSUES THE PETITION PRESENTS ARE NOT OPEN QUESTIONS OF FEDERAL LAW

A. There Is No Open Question Regarding the Effect of Subsequent Regulatory Events on a Regulatory Decision's Preemptive Effect

McNellis states, without supporting citation: "Courts have struggled to determine whether to 'freeze' the misbranding analysis or whether and to what extent they should consider subsequent regulatory events." (Pet. at 30.) Although it is unclear which courts McNellis believes have "struggled" with this question, the Third Circuit here expressed no

doubt regarding the analytical impropriety of basing a preemption determination on regulatory actions that occur after the event on which a plaintiff bases her claim for relief. Consistent with the law as established by this Court, the Third Circuit properly analyzed the conflict issue based on FDA's requirements that applied when DeAngelis used Zoloft.

This Court's decision in *Geier v. American Honda Motor Co.*, 529 U.S. 861 (2000), makes clear that an agency's later decision to amend a regulatory requirement does not retroactively obliterate the preemptive effect the pre-amendment regulation had with respect to events that occurred while it was in effect. The Court in *Geier* held that the Department of Transportation's requirement that a certain percentage of automobiles made in the year in question must have either airbags or some other passive restraint preempted a claim that all automobiles made in that year should have had airbags. The Court so held even though the agency had concluded that all automobiles made after a specified later date must have airbags.

The Third Circuit plainly understood and applied this rule, stating that, for purposes of determining the presence or absence of a conflict, "[o]ur focus is on the period before the two deaths that are the subject of the actions before us." 521 F.3d at 273. The court did note that FDA's subsequent analyses of adult suicidality data, and its affirmation that the data still did not establish an association between SSRIs and adult suicidality, refuted two of McNellis's anti-preemption arguments. First, it noted, FDA's subsequent findings confirmed that subsequent events had not, as McNellis claimed, caused FDA to alter its

previous conclusions that SSRIs are not associated with adult suicidality. *Id.* Second, it noted, FDA's conclusions based on review of all data as of 2007 refuted the suggestion that "FDA lacked information that would have dissuaded it from rejecting an adult suicidality warning for Zoloft, Paxil, or generic paroxetine in 2003." *Id.* at 273-74.

The Third Circuit's decision thus does not present any open question concerning the consideration of subsequent regulatory events. The court properly concluded that (i) the presence or absence of conflict must be determined based on federal requirements in effect during the relevant period, and (ii) subsequent events—particularly agency decisions reaffirming the requirement in effect during the relevant period—are relevant only to the extent they confirm or elucidate the requirements in effect during the relevant period. This holding is fully consistent with this Court's holding in *Geier*, and it does not conflict with any appellate decision of which we are aware.

B. There Is No Open Question Whether FDA or a Court Should Decide, in the First Instance, If FDA Has Been Defrauded and Otherwise Would Have Required a Different Warning

McNellis erroneously claims that the Third Circuit, relying on *Buckman Co. v. Plaintiffs' Legal Committee*, 531 U.S. 341 (2001), refused to consider whether information regarding adult suicidality was not disclosed to FDA. In fact, however, the Third Circuit did consider that contention and stated that the nondisclosure claim, "if supported by sufficient evidence, should be brought before the FDA." 521 F.3d at 272. The court also found the nondisclosure

claim factually refuted by FDA's regulatory actions subsequent to DeAngelis's demise. *Id.* at 273-74. These rulings were correct under the well-settled doctrine of primary jurisdiction and the regulatory evidence before the court.

This Court explained the primary-jurisdiction doctrine in *Far East Conference v. United States,* 342 U.S. 570 (1952), as the

> firmly established [principle] that in cases raising issues of fact not within the conventional experience of judges or cases requiring the exercise of administrative discretion, agencies created by Congress for regulating the subject matter should not be passed over. This is so even though the facts after they have been appraised by specialized competence serve as a premise for legal consequences to be judicially defined. Uniformity and consistency in the regulation of business entrusted to a particular agency are secured, and the limited functions of review by the judiciary are more rationally exercised, by preliminary resort for ascertaining and interpreting the circumstances underlying legal issues to agencies that are better equipped than courts by specialization, by insight gained through experience, and by more flexible procedure.

Id. at 574-75. Contrary to those principles, McNellis would have a court determine in the first instance whether (i) some document or datum that allegedly

was not provided to FDA should have been provided to FDA and, (ii) when considered in conjunction with the totality of other information the agency already had considered, would have caused FDA to reverse its judgment that the totality of available information did not constitute "reasonable evidence of an association" between SSRIs and suicidality.

These determinations lie at the very heart of FDA's expertise and congressionally delegated authority. In fact, this Court has recognized, in addressing the similar question of FDA's authority to decide what is or is not a "new drug" under the 1962 amendments to the FDCA, that "[t]he heart of the new procedures designed by Congress is the grant of primary jurisdiction to FDA, the expert agency it created." *Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 627 (1973).

Other courts have recognized that interpreting medical and scientific evidence, and determining how best to describe the available evidence in drug labeling, must in the first instance be left to FDA. *See, e.g.*, *Sandoz Pharm. Corp. v. Richardson-Vicks, Inc.*, 902 F.2d 222, 231 (3d Cir. 1990) (finding that a court could not properly decide whether listing an ingredient in cough syrup as "inactive" was false, because to do so "would require us to usurp administrative agencies' responsibility for interpreting and enforcing potentially ambiguous regulations"); *Bernhardt v. Pfizer, Inc.*, Nos. 00 Civ. 4042 LMM, 00 Civ. 4379 LMM, 2000 WL 1738645, at *3 (S.D.N.Y. Nov. 22, 2000) (referring to FDA, under the primary-jurisdiction doctrine, the question of whether the results of a scientific study triggered a duty to provide a particular warning, because that decision "has been

squarely placed within the FDA's informed expert discretion"); *cf. Henley v. FDA*, 77 F.3d 616, 621 (2d Cir. 1996) (deferring to FDA's determination of whether oral contraceptives should include a cancer warning, because "FDA possesses the requisite know-how to conduct such analyses, by sifting through the scientific evidence to determine the most accurate and up-to-date information regarding a particular drug"); *Premo Pharm. Labs., Inc. v. United States*, 629 F.2d 795, 803 (2d Cir. 1980) (noting that the question of whether a medication is safe and effective "is to be determined by the FDA which, as distinguished from a court, possesses superior expertise"). Thus, the Third Circuit's treatment of the suggestion that information allegedly withheld from FDA was reportable under FDA regulations and would have altered FDA's conclusions and requirements was fully consistent with the doctrine of primary jurisdiction as recognized and applied by this Court and others.

The Third Circuit also found that—irrespective of whether the nondisclosure claim should be presented to a court in the first instance—recent regulatory developments refute any suggestion that FDA was misled into concluding that SSRIs are not associated with adult suicidality. Even after scrutinizing and evaluating all information and data available as of 2007, including data on which McNellis relies, FDA's judgment continued to be that SSRIs are not associated with adult suicidality. As the Third Circuit found, this conclusion negates any suggestion that Petitioners had identified any information "that would have dissuaded [FDA] from rejecting an adult suicidality warning for Zoloft, Paxil, or generic paroxetine in 2003." 521 F.3d at 273-74.

In addition to finding that the nondisclosure claim should be presented to FDA in the first instance, the Third Circuit also noted that a claim that preemption should be defeated due to alleged withholding of information from FDA "borders on the charge that GSK defrauded FDA by manipulating or withholding such information." 521 F.3d at 272 (citing *Buckman*). The Third Circuit recognized that such a charge implicated, and should be rejected because of, several concerns that this Court expressed in finding preemption in *Buckman*.

As this Court found in *Buckman*, allowing "fraud on the FDA" claims would cause manufacturers to "have an incentive to submit a deluge of information that the Administration neither wants nor needs, resulting in additional burdens on the FDA's evaluation of an application." 531 U.S. at 351. The same problem would be created if plaintiffs could defeat preemption in every case merely by alleging that FDA would have mandated a different warning had the manufacturer provided just one more document or just one more datum. If preemption could be so easily evaded, no manufacturer regulated by FDA could preserve preemption without forwarding to FDA every datum and every document that any plaintiff could conceivably allege would have caused FDA to make a different decision. This would create the same, or an even greater, "deluge of information that the Administration neither wants nor needs" that in *Buckman* this Court found would create impermissible interference with the accomplishment of FDA's goals.

Buckman thus supports the Third Circuit's conclusion that McNellis's nondisclosure claim must be

presented to FDA in the first instance. McNellis does not claim she ever did so.

Accordingly, whether based on primary jurisdiction, a finding of preemption under *Buckman*, or both, the Third Circuit's ruling correctly implemented the federal judicial policy of avoiding incursion into the core subject matter of an expert agency's competency and avoiding interference with the agency's decision-making process. The court's implementation of that policy does not present any open question of federal law.

III. THE DECISION BELOW WAS CORRECT

A. Contrary to McNellis's Contention, Preemption Here Is Not Based on "Hypothetical Misbranding," but on the Direct Conflict Created by Her Claim That Pfizer Should Have Provided a Warning That FDA Rejected for Federal Safety Reasons

McNellis's criticism of the Third Circuit's decision rests largely on her mischaracterization of the conflict found by the court as based on "hypothetical misbranding." (Pet. at 28-30.) But the Third Circuit did not base its preemption finding on any "hypothetical misbranding." Instead, the court found preemption because of the actual, direct conflict between (i) FDA's finding that reasonable evidence did not support a warning stating that Zoloft is associated with suicide and (ii) McNellis's claim that state law required just such a warning. The court made crystal clear that this direct conflict, rather than the possibility of prosecution for misbranding, was the basis of its preemption ruling:

> Because the standard for adding a warning to drug labeling is the existence of "reasonable evidence of an association of a serious hazard with a drug," 21 C.F.R. § 201.57(e), and the FDCA authorizes the FDA to prohibit false or misleading labeling, a state-law obligation to include a warning asserting the existence of an association between SSRIs and suicidality directly conflicts with the FDA's oft-repeated conclusion that the evidence did not support such an association.

521 F.3d at 271; *see also id.* at 275 ("FDA's rejection of the warning plaintiffs proffer preempts a state-law action premising liability on a drug manufacturer's failure to include such a warning in the drug labeling").

By arguing that the presence or absence of a conflict turns on whether the federal government would have successfully prosecuted Pfizer for misbranding had Pfizer ignored FDA's requirement and unilaterally implemented the warning McNellis advocates, McNellis seeks a ruling that preemption requires showing not only that state law conflicts with federal law, but that the federal government would have successfully prosecuted a failure to comply with the federal requirements. She fails to cite even one case, however, applying any such requirement.

In fact, this Court and others have either expressly or impliedly rejected her argument. In *Geier*, for example, this Court rejected an argument that preemption should not obtain because the defendant

might not violate a state tort-law requirement and might not be sued for the violation:

> Petitioners ask this Court to calculate the precise size of the "obstacle," with the aim of minimizing it, by considering the risk of tort liability and a successful tort action's incentive-related or timing-related compliance effects. . . . But this Court's pre-emption cases do not ordinarily turn on such compliance-related considerations as whether a private party in practice would ignore state legal obligations—paying, say, a fine instead—or how likely it is that state law actually would be enforced. Rather, this Court's pre-emption cases ordinarily *assume* compliance with the state-law duty in question.

529 U.S. at 882. The same considerations apply to McNellis's argument that preemption here should turn on whether FDA would enforce its regulations if Pfizer were to violate them, and her argument fails for the same reasons.

McNellis's argument, drawn to its logical conclusion, would preclude implied preemption even of a state statute outlawing the payment of federal income taxes unless (i) an individual complied with the state law by refusing to pay federal taxes; (ii) federal officials prosecuted the individual for failure to pay federal taxes; and (iii) the prosecution resulted in a guilty verdict. McNellis's adoption of this broad, unsupported, and illogical position underscores the acute conflict her claims create.

McNellis's focus on what she claims to be examples of other manufacturers' having instituted labeling changes without being prosecuted for misbranding is misguided for similar reasons.[5] As this Court held in *Geier*, preemption does not "turn on such compliance-related considerations as whether a private party in practice would ignore" the relevant requirements. 529 U.S. at 882. Accordingly, other manufacturers' alleged disobedience of FDA's requirements, even if real, does not negate the preemptive effect of those requirements.

The proper analysis, which the Third Circuit employed here, focuses on (i) ascertaining the relevant state and federal requirements and (ii) determining whether they conflict. FDA's determination that reasonable evidence did not support a warning stating that Zoloft is associated with adult suicidality, and the agency's before-and-after mandates that Pfizer use only the exact suicidality warnings dictated by the agency, created federal requirements in actual, direct conflict with McNellis's claim that state law required Pfizer to provide the very warnings that FDA had rejected. Whether the federal government would have brought a misbranding action had Pfizer

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[5] McNellis's characterization of labeling changes allegedly implemented by the manufacturers of Effexor and Paxil in 2003 and 2006, respectively, is wrong. The premise—that FDA permitted those labels to remain as amended by their manufacturers—is wrong. FDA in 2004 required ***all*** SSRI labels to include materially identical warnings concerning pediatric suicidality, and in 2007 required ***all*** SSRI labels to be revised to reflect FDA's reaffirmation that there is no association between SSRIs and increased adult suicidality. Also, that FDA did not need to prosecute a misbranding action to enforce its labeling requirements confirms the agency's power to require labeling changes.

ignored FDA's requirements and adopted the warning advocated by McNellis, whether such an enforcement action would have been successful, and the purported disobedience of other manufacturers in other instances involving other drugs, do not affect this analysis.

B. The Conflict Created by McNellis's Claim Is Actual, Not Hypothetical

Relying further on her erroneous assertion that the Third Circuit's finding of preemption here is "based on misbranding," McNellis suggests that, because a misbranding action is only a hypothetical possibility that could have occurred had Pfizer unilaterally adopted the warning she advocates, the preemptive conflict recognized by the Third Circuit is impermissibly hypothetical. As shown above, however, the Third Circuit based its ruling on the actual, direct conflict between FDA's requirements and McNellis's state-law claims. That conflict is at least as real as the one this Court addressed in *Geier*, where preemption was based on the conflict between, on one hand, the Department of Transportation's determination that the various car models made in specified years should have a mix of restraint devices and, on the other, the plaintiff's claim that all cars made without airbags in those years were defective. 529 U.S. at 881. The Third Circuit's ruling thus did not rely on any impermissibly hypothetical conflict.[6]

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[6] Contrary to McNellis's assertion, the Third Circuit did not hold that a "hypothetical conflict can form the basis for conflict preemption." (Pet. at 16-17.) Instead, the court noted that the "scarcity of actual conflict cases has led the Justices to pose hypothetical conflicts," and then discussed cases in which this

In arguing to the contrary, McNellis relies on inapposite authority addressing the quintessentially hypothetical conflict presented by a facial challenge to a state statute. (*See* Pet. at 17 (citing *Rice v. Norman Williams Co.*, 458 U.S. 654, 659 (1982)).) In *Rice* the Court addressed a facial challenge to a California liquor importation law that the defendant argued was preempted by the Sherman Antitrust Act. *Id.* at 657-58. In determining whether the Sherman Act preempted the California statute, the Court noted that "a state statute, when considered in the abstract, may be condemned under the antitrust laws only if it mandates or authorizes conduct that necessarily constitutes a violation of the antitrust laws ***in all cases***." *Id.* at 661 (emphasis added). Because compliance with the California statute would have resulted in antitrust violations only in certain hypothetical situations, not in all cases, the Court held that the statute was not preempted on its face. *Id.* at 661-62. In so holding, however, the Court noted that any ***particular*** application of the statute in a manner violating federal antitrust laws would be subject to "scrutiny under the Sherman Act." *Id.* at 662.

Here, Pfizer does not contend that the New Jersey Products Liability Act, N.J.S.A. 2A: 58C-1, *et seq.*, is preempted on its face due to the potential for hypothetical product liability claims in conflict with FDA requirements. Instead, Pfizer contends, and the Third Circuit found, that the particular claims ad-

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Court had posed hypothetical conflicts as illustrations of preemptive conflicts. 521 F.3d at 266-67. The court did not say that a hypothetical conflict could form the basis of preemption; and, as noted above, the conflict the court found was not hypothetical.

vanced by McNellis under the state law conflict with FDA's Zoloft-specific labeling requirements. *Rice* therefore is inapposite.

C. This Court's Decision in *Sprietsma* Supports Preemption

Relying on this Court's decision in *Sprietsma*, McNellis argues that FDA did not regulate Zoloft's suicidality warnings, that FDA merely failed to act with respect to suicidality warnings such as the one she advocates, and that a federal agency's failure to act does not create a federal requirement capable of preempting state law. (Pet. at 22-28.) But that argument ignores the sharp difference between the federal agency inaction in *Sprietsma* and the federal agency action here. *Sprietsma* in fact confirms the correctness of the Third Circuit's decision in this case.

In *Sprietsma* this Court ruled that the Coast Guard had declined to promulgate any safety regulation governing boat propellers and that "the refusal to regulate propeller guards" did not preempt claims that boat propellers were defectively designed. *Sprietsma*, 537 U.S. at 68. Here, in stark contrast, FDA did not refuse to regulate Zoloft labeling regarding suicidality; instead, FDA required that the labeling include specific suicidality language that differed in content and location from the language McNellis argues state law required, and FDA prohibited McNellis's advocated language by requiring that the labeling be "identical to" the agency-specified language.

This Court addressed a similar distinction in *Sprietsma* itself. The Court noted that, in contrast to

Geier, where conflict preemption existed because the Department of Transportation had elected not to require airbags in all cars, but had provided for airbags as one of several options, the Coast Guard in *Sprietsma* had not imposed any propeller-guard requirement at all. 537 U.S. at 67. In short, the presence in *Geier* of a federal regulation requiring either airbags or other passive restraints supported preemption of a state-law all-airbag requirement, whereas the absence in *Sprietsma* of any Coast Guard regulation either requiring or prohibiting propeller guards under any set of circumstances could not support preemption. Here, because FDA required specific suicidality warnings, and prohibited any other suicidality warning, for Zoloft, both *Geier* and *Sprietsma* support the Third Circuit's finding of preemption.

This Court's decision last term in *Riegel v. Medtronic, Inc.*, 128 S. Ct. 999 (2008), further confirms that FDA's imposition of suicidality labeling requirements when approving the original and supplemental Zoloft NDAs constituted affirmative regulatory action, not a "refusal to regulate." In *Riegel*, FDA had specified the labeling for a medical device when it approved the manufacturer's premarket approval application ("PMA") for the device under the Medical Device Amendments of 1976 ("MDA"). This Court held that the MDA's express preemption provision preempted state-law tort claims alleging that the FDA-specified warnings were inadequate. In rejecting the plaintiff's argument that FDA's premarket approval did not impose "requirements" under the MDA, the Court stated:

> Premarket approval . . . imposes "requirements" under the MDA. . . . Unlike general labeling duties, premarket approval is specific to individual devices. And it is in no sense an exemption from federal safety review—it *is* federal safety review. . . . FDA requires a device that has received premarket approval to be made with almost no deviations from the specifications in its approval application . . . .

128 S. Ct. at 1007.

Here, likewise, the FDA-specified suicidality warnings are specific to an individual drug, Zoloft, and to a particular risk, suicidality. Like FDA approval of a PMA for a medical device with FDA-specified labeling, FDA approval of an NDA for a drug with FDA-specified labeling "is in no sense an exemption from federal safety review—it *is* federal safety review." As with a medical device that has received PMA approval, a drug that has received NDA approval must be labeled with "no deviation from the [labeling] specifications in its approval application." Thus, just as FDA's actions in *Riegel* imposed regulatory requirements and were not a "refusal to regulate," FDA's actions here imposed regulatory requirements and were not a "refusal to regulate."

McNellis's argument also fails because it ignores that FDA's rejection of a more dire warning in favor of a less dire warning is an act of regulation aimed at fulfilling the agency's dual responsibilities of ***both*** protecting ***and*** promoting public health not just by ensuring that medications are reasonably safe, but

also by ensuring their availability and optimal use. 21 U.S.C. § 393. FDA's labeling regulations reflect the goal of ensuring beneficial use (and avoiding over-warning) by requiring that warnings be supported by "reasonable evidence of an association" between medication and hazard. 21 C.F.R. § 201.57(e). The agency has for decades interpreted this requirement to preclude a warning in the absence of "evidence . . . on the basis of which experts qualified by scientific training and experience can reasonably conclude that the hazard is associated with the use of the drug." 44 Fed. Reg. at 37447. FDA repeatedly has stated that it would not mandate scientifically unsubstantiated SSRI suicidality warnings, because such warnings can harm patients by deterring beneficial use and by diluting the impact of scientifically supported warnings:

> Under-utilization of a drug based on dissemination of scientifically unsubstantiated warnings, so as to deprive patients of beneficial, possibly lifesaving treatment, could well frustrate the purposes of federal regulation as much as over-utilization resulting from a failure to disclose a drug's scientifically demonstrable adverse effects. Further, allowing unsubstantiated warnings may also diminish the impact of valid warnings by creating an unnecessary distraction and making even valid warnings less credible.

(JA 268.)

In sum, by repeatedly finding that reasonable evidence of an association between SSRIs and suicidality did not exist, and by requiring Pfizer to provide the specified suicidality warnings, rather than others, FDA in no sense engaged in what McNellis calls a "refusal to regulate" Zoloft suicidality warnings. To the contrary, it regulated with great specificity and care.

CONCLUSION

The petition for writ of certiorari should be denied.

Respectfully submitted.

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